

Introduction

It is a winter day and Mr. Jones, a 45-five-year-old man suffering from chronic renal failure has just arrived at his regional dialysis center. He comes here three times a week, each time for four hours, to be connected to a hemodialysis machine. These treatments are necessary for Mr. Jones to stay alive. During each 4-hour treatment his entire blood volume will pass through the artificial kidney machine about 14 times for purification. On this same day, many miles away, an American black bear slumbers in its wintery cave. The bear will remain there dormant for up to five months during which time this animal will not eat, drink, defecate or urinate. Although dormant, the bear still has an active metabolic rate about 50% of normal. Yet despite having no urine output for this prolonged period of time, the bear will not suffer any of the manifestations of renal failure experienced by Mr. Jones. How has the bear's metabolic machinery adapted to such a prolonged state of functional renal failure? Can we learn new approaches for the prevention and/or treatment of chronic renal failure from such a natural animal model?

Natural selection is the mechanism underlying the process of evolution. Changing environmental conditions select out animals whose metabolic/physiologic characteristics confer on them a survival advantage. Evolution can be considered a natural experimental process in which over billions of years countless animal design features have been tested. In some cases, an animal group or species has evolved a set of biochemical/physiological features natural and adaptive for that animal but quite abnormal for humans. For example, many species of birds have extremely

high blood glucose concentrations which are clearly natural and adaptive for these birds but would be considered quite abnormal and in fact in the diagnostic range for diabetes if found in humans. Despite these high blood glucose levels, these birds do not suffer vascular and renal complications as observed in humans with diabetes. Can the study of these avian models give us insights into the pathogenesis of diabetic complications in humans? Patients with hepatic disease frequently suffer from ammonia neurotoxicity. Fish on the other hand, are ammonia tolerant as compared to mammals. Can fish teach us how to prevent ammonia neurotoxicity? In this book, a natural animal model is defined as an animal group or species that possesses biochemical/physiological characteristics natural for that animal but pathological for humans. By using these models, we take advantage of all the “research” that nature has already performed in animal design testing and selection. The premise of this book is that by studying natural animal models we can gain valuable insights into the etiology and treatment of various clinical disorders.

Animals have been used extensively as subjects in medical research, but not generally in their natural state. One approach is to induce a disease in the animal either through pharmacologic or genetic techniques. Sometimes a disease occurs spontaneously in a few members of an animal group and then these animals can be bred to create a colony of disease-afflicted animals. With these models the implicit assumption is made that the disease is similar to that observed in humans. We can use such models to investigate pathogenic mechanisms underlying the disease and also to explore possible treatment options. Natural animal models do not suffer from a disease and hence provide a different perspective. With these models, we can examine biological solutions to clinical disorders that nature has tested through the cauldron of evolution and proven to be effective. Birds, which naturally have chronically high blood glucose levels, do not suffer from diabetes. The question we must ask of such a natural model is how do these birds tolerate blood glucose concentrations, which in the human are associated with pathological consequences. The natural model is living proof that a biological answer to this question is available.

Most biochemical/physiological processes are multifactorial. For example, consider the hepatic synthesis of urea in the mammal. Production of urea in the liver serves to detoxify ammonia liberated as a result of amino acid catabolism. In addition, urea is also an important component of systems involved in nitrogen and water conservation. Some of the produced urea is transferred across the gut wall where the nitrogen can

be salvaged via the action of bacteria, and some of the urea is transferred across the wall of the kidney tubule into the surrounding tissue where its accumulation aids in water reabsorption. This concept of multifunctionality is important. If we were to consider urea only as a vehicle for ammonia detoxification, then this molecule might be considered a poor choice since it is metabolically expensive to synthesize. However, since this same molecule also functions in systems designed to conserve water and nitrogen then its "value" becomes enhanced considerably.

Multifunctionality is an example of the economy of animal design characteristics. If we were to consider a single animal system in isolation, we would probably conclude that it was not designed optimally in terms of the matching of structure and function. However, if we consider this same system in light of all the functions that it serves we would conclude that it was optimally designed to fulfill these multiple functions. The solutions to clinical disorders that natural animal models give us represent adaptations that have evolved within this context of multifunctionality of body systems. In contrast, consider the animal that has been induced to have a specific disease. We might design a drug to treat that disease based on studies done in such an animal model. This drug will probably have a number of unexpected side effects since the drug has only been designed to affect one of the functions of the targeted receptor or molecule thought to be involved in the disease process. Since multifunctionality is generally the rule, side effects will arise from the drug interfering with the other as yet unidentified functions of that receptor or molecule. On the other hand, the solutions that nature gives us will not have side effects since they would have evolved within a multifunctionality framework.

We might consider that a bird and a turtle are so different from humans that such natural animal models have no relevance to clinical disorders. However, the cornerstone of Darwin's theory is that all organisms had common ancestors and that probably all life on Earth started from a single origin of life. Some basic genes of higher organisms can be traced all the way back to homologous genes in bacteria. In addition, despite the incredible diversity of animals there are clearly underlying common design features. For example, mammals, birds, reptiles and fish appear to have similar systems for conserving body nitrogen. All vertebrates and even some insects appear to respond to an increase in protein intake with similar changes in excretory function. Antifreeze protein, a molecule designed to prevent ice crystal damage in body fluids, is present in the antarctic perch and the arctic cod. However, antifreeze protein evolved separately in these

two fish. Hence they independently developed a shared solution to a similar environmental challenge. These common design features arise through the process of convergent evolution, which can be simply characterized as similar problems giving rise to similar solutions. However, the best justification for the use of natural animal models is that these models clearly teach us what is biologically possible. As stated by Janine Benyus in her book, "Biomimicry", after 3.8 billion years of evolution nature has learned what works, what is appropriate and what lasts (Benyus, 1997).

This book is organized into six chapters each one dealing with a specific clinical disorder and a description of possible natural animal models for studying that disorder. The choice of clinical disorders has been based simply upon the author's awareness of possible natural animal models for these specific disorders. This book is not meant to be encyclopedic but rather the intent of this book is to foster a comparative physiological approach to clinical problem solving rooted in the use of natural animal models. The clinical disorders and models described in the different chapters serve as examples of this approach.

Each chapter begins with a review of a clinical disorder followed by a discussion of natural animal models for that clinical disorder. The chapters are generally independent of each other and what follows is a brief overview of the clinical disorders covered and a listing of the natural animal models discussed.

The focus of Chapter 1 is on diabetes mellitus, which is becoming almost epidemic in developed countries. Birds, in general, as already mentioned, are a good natural animal model for this disease. Chronic renal failure is reviewed in Chapter 2 and the bear represents a natural model for this disorder. The bear completely recycles its nitrogenous wastes during its dormant period and does not develop any manifestations of renal failure. In Chapter 3 the focus is on atherosclerotic vascular disease. Certain species of fish are a very relevant natural model for this disorder. Salmon develop coronary artery thickenings resembling the early form of mammalian atherosclerosis. Presumably these coronary vascular changes in the salmon are adaptive. However, the lesions in the fish, unlike those in the human, do not show progression. When patients are confined to bed they develop disuse muscle atrophy as well as disuse osteoporosis. These clinical disorders are considered in Chapter 4. The bear is a wonderful natural model for studying these problems since this animal suffers only minor muscle atrophy and osteoporosis during its long dormant period. The problem of ammonia toxicity, which is observed primarily in patients with liver failure or inherited urea

cycle enzyme deficiencies, is reviewed in Chapter 5. Fish can be considered a natural animal model since they have evolved adaptations allowing them to tolerate blood ammonia levels that would be lethal in humans. Chapter 6 deals with the problem of hypoxia and ischemia and primarily focuses on the effects of hypoxia/ischemia on the brain. There are a number of natural animal models relevant to this disorder. These models include the turtle, carp and species of birds that fly at high altitudes.

Physiology is a valuable discipline with which to frame important questions concerning the way humans function. Comparative physiology enables us to see that human functions are not unique but are shared at least in part by a variety of animals. The use of natural animal models is simply an extension of this concept. When a human function becomes abnormal because of a disease process, can we find an animal, which has solved a similar problem through the pressures of natural selection? Can that solution be transferred in part or whole to the human with that abnormal function? It is my hope that this book will convince the reader that the answers to these questions are yes.

Reference

Benyus, J.M., 1997. *Biomimicry: Innovation Inspired by Nature*. William Morrow and Company, Inc., New York.